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(54) Title: METHOD FOR USING NUTRIENT-CONTAINING LIPOSOMES IN HYPERALIMENTATION

(57) Abstract

A method for intravenous alimentation wherein nutrient-containing bilayer membrane vesicles dispersed in a physiologically compatible carrier are introduced into the bloodstream to satisfy at least a substantial portion of the subject's caloric requirements.

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METHOD FOR USING NUTRIENT-CONTAINING LIPOSOMES IN HYPERALIMENTATION

BACKGROUND OF THE INVENTION

This invention relates to a method for providing nutrition intravenously using a physiologically compatible, nutritionally effective liquid dispersion of liposomes which optionally encapsulate a nutrient composition.

In the field of hyperalimentation, a persistent and troublesome problem has been delivering nutrition to an intravenously-fed patient in sufficient amounts to sustain health while at the same time keeping the total volume of intravenous fluid introduced into the patient within certain bounds dictated, in part, by the condition of the patient. For example, in patients suffering from cardiovascular dysfunction, the balancing of nutritional requirements with inherent limitations on how much fluid can be introduced without unduly burdening the cardiovascular system is particularly difficult.

A common approach to this problem is to maximize the caloric content per unit volume of the intravenous fluid, thereby permitting more calories to be

introduced using less fluid. Increasing nutrient concentration in this fashion can be greatly restricted by limits on the permissible osmolality of the intravenous fluid. Increases in the nutrient concentration of the fluid are associated with a concomitant increase in the fluid's osmolality, until a point is reached where additional increases in concentration (and osmolality) make introducing the fluid via conventional intravenous hookups impractical.

For example, there are presently two main solutions for intravenous alimentation, P-900 and C-1800. The osmolality of the former is 900 milliosmols (mosmols), whereas that of the latter is 1800 mosmols. Each solution contains essential and non-essential amino acids, but the main difference between them as to osmolality and caloric content is that C-1800 contains approximately 250 grams of glucose per liter while P-900 contains about 50 grams of glucose per liter. As a result of the high osmolality, which can lead to severe phlebitis in the peripheral veins, C-1800 must be given by a central line via the subclavian or internal jugular vein. Besides the risk involved and skill required in placing such a central line, careful nursing care must be given to maintaining the central line.

P-900, on the other hand, can be given peripherally but its caloric content is only 350 cals/liter, as opposed to 1150 cals/liter for C-1800. The caloric needs of a hospitalized patient vary considerably, but requirements in excess of 3000 cals/day are not unusual, and some patients may require as many as 5-6,000 cals/day. P-900 by itself cannot prevent weight loss in such patients, even when supplemented with intralipids. (Intralipids are fat emulsions which can be given separately from the P-900 or C-1800 solutions.) A disadvantage to both solutions is that to provide

1200 calories in the P-900 solution and 3000 calories in the C-1800 solution, three liters of fluid must be given per day. In many patients, for example, those with compensated congestive heart failure, this amount of fluid is not tolerable.

Another drawback to existing methods of intravenous feeding is evident when fat emulsions such as INTRALIPID® (a product of Miles Laboratories, Berkeley CA) and LIPOSYN® (a product of Abbott Laboratories, North Chicago IL) are included in the hyperalimentation fluid. In such conventional intravenous fat emulsions, aggregation and fusion of lipid globules are typically observed over time, the extent of such phenomena depending on a complex interaction of several variables, including the nature and the concentration of electrolytes in the carrier, the order in which various ingredients are added during preparation of the intravenous fluid, and the electrical charge carried on the surface of the globules. Once aggregation has occurred, the lipid globules do not readily dissociate after they are introduced into the bloodstream. As a consequence, the stability of intravenous fat emulsions, particularly during prolonged storage, has been questioned. See, e.g., Black & Popovich, "Stability of Intravenous Fat Emulsions," ARCH. SURG. 115: 891 (1980); Pamperl & Kleinberger, "Stability of Intravenous Fat Emulsions," ARCH. SURG. 117: 859-60 (1982).

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a method of hyperalimentation which can be employed even under circumstances requiring that fluid intake be controlled, as with patients suffering impaired cardiovascular function.

It is another object of the present invention to provide a method for intravenous alimentation which

does not entail the problem of undue osmolality encountered with conventional hyperalimentation techniques which utilize high-concentration intravenous fluids.

It is a further object of the present invention to provide a method for supplying intravenous nutrition which requires little prior manipulation of the intravenous fluid and which entails minimal side effects for the patient.

It is yet another object of the present invention to provide a hyperalimentation method which maximizes the uptake in vivo of nutrient values contained in the intravenous fluid.

In accomplishing the foregoing objects, there has been provided, in accordance with one aspect of the present invention, an intravenous alimentation method comprising the step of introducing into the bloodstream of a mammal a hyperalimentation fluid comprising a physiologically compatible carrier having dispersed therein a nutritionally effective amount of nutrient-containing vesicles, each vesicle comprising a bilayer membrane. In preferred embodiments of the present invention, the vesicles in the hyperalimentation fluid are comprised of lipid material sufficient to satisfy a substantial portion of the mammal's intravenous caloric requirements. In another preferred embodiment, the vesicles encapsulate a nutrient solution suitable as an intravenous caloric source for the mammal.

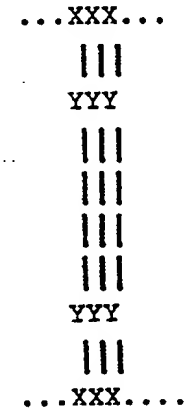
Other objects, features, and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and specific examples which follow, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from the following description.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

To overcome the aforementioned drawbacks associated with prior art intravenous feeding methods, applicant has discovered that it is possible in effect to "shield" a significant portion of the osmolality of a hyperalimentation fluid by entrapping the nutrient fraction of the fluid within microscopic vesicles which have bilayer lipid membranes. Such vesicles are called "liposomes," although the latter term has occasionally been used loosely to refer as well to lipid globules, such as are found in certain fat emulsions. As used in this application, the term "liposome" refers to a vesicle bounded by a bilayer lipid membrane, as set out in greater detail below.

As stated previously, in the present invention liposomes are used as vehicles for delivering the nutrient fraction, via the bloodstream, to targeted organs within the body. Before the aforementioned "shielding" effect and other features of the present invention are explained in greater detail, it must be understood the liposomes are vesicles, generally spherically shaped, formed from one or several concentric layers (lamellae) of lipid molecules, i.e., compounds having a lipophobic hydrophilic moiety and a lipophilic hydrophobic moiety. The lamellae of a water-soluble liposome are formed of at least one bimolecular lipid layer (which lipid can be represented hereinafter by the formula XY, wherein X is the hydrophilic moiety and Y is the hydrophobic moiety), the molecules of this layer being so oriented that the hydrophilic functions thereof stay in contact with the aqueous phase. Since the liposomes lamellae are separated from each other by a water film, they have a wall-like structure which can be schematically represented, in section, by a series of molecular composites XY--YX stacked together in the plane of the paper.

The size of the liposome vesicles is variable and depends in part on the method used for their manufacture. In general, they range in diameter between about 25 and 3,000 nm, and the lipid film constituting the liposome wall is about 3 to 10 nm thick. A liposome in this range may have a monolamellar envelope, that is, a monolayer of the following molecular association:



Nevertheless, a given liposome may comprise hundreds of layers, each with the structure of the above-depicted monolayer.

Liposomes in which most of the constituent lipid participates in a plurality of internal lamellae are commonly termed "multilamellar vesicles" (MLV's), and can be prepared, for example, using the method of Bangham et al., J. MOL. BIOL. 13: 238-52 (1965), the contents of which are incorporated herein by reference. MLV's generally range in size from about 0.2 to about 2 microns.

Single-compartment liposomes characterized by a large surface-to-encapsulated-volume ratio can be prepared, for example, by sonication of multilamellar liposomes as described by Gregoriadis, "Liposomes," in DRUG CARRIERS IN BIOLOGY AND MEDICINE, 287-341 (G. Gregoriadis ed. 1979), the contents of which are incor-

porated herein by reference. Such liposomes, sometimes called "sonicated unilamellar vesicles" in the art, are herein designated "small unilamellar vesicles" (SUV's), in recognition of the fact that they can be prepared by other known methods than sonication, for example, by passing MLV's through a French press or by the ethanol injection of lipid in an aqueous phase. A review of the preparative methodology is presented by Deamer and Uster, "Liposome Preparation: Methods and Mechanisms," in LIPOSOMES (M. Ostro ed. 1983), the contents of which are incorporated herein by reference. SUV's prepared by these methods range in size from about 0.02 to about 0.15 microns.

A third category of liposomes includes vesicles produced by the "reverse-phase evaporation method" described by Szoka, Jr., and Papahadjopoulos, "Procedure for Preparation of Liposomes with Large Internal Aqueous Space and High Capture by Reverse-Phase Evaporation," PROC. NATL. ACAD. SCI. USA 75: 4194-98 (1978). The aforementioned types of liposomes differ in terms of their ability to entrap aqueous material, their respective aqueous space-to-lipid ratios, and their relative affinities for specific targets in vivo.

In general, the larger a liposome, and the fewer layers it has, the more liquid it can encompass. Since the liquid in which a liposome is dispersed can differ compositionally from that contained within the liposome itself, liposomes are potentially useful as biodegradable, relatively non-toxic vehicles for administering a pharmaceutically active agent to a living organism without the risk of prematurely degrading the agent as might occur, for example, in the gastrointestinal tract. See, generally, Gregoriadis, supra.

But liposomes have never been used, to applicant's knowledge, for the delivery of nutrition

during intravenous feeding. Yet by encapsulating a nutrient solution that contains, for example, a carbohydrate which can serve as a source of energy when taken up in vivo, it is possible, in accordance with the present invention, to mitigate substantially the problem encountered in the prior art of supplying sufficient calories via intravenous feeding without overburdening the cardiovascular system with intravenous fluid. Specifically, the delivery of nutrients intravenously via a dispersion of liposomes in an appropriate carrier medium, as provided by the present invention, permits a reduction in the number of particles in the intravenous fluid medium relative to the number of particles that would otherwise be present if a nutrient-containing solution were mixed, unencapsulated, into the carrier, as in the prior art.

Because the osmolality of a fluid is a function of the number of distinct particles contained therein, the reduction in particle number which is effected by encapsulating the nutrient solution "shields" the actual number of solute (nutrient) molecules introduced into a peripheral vein with each volume unit of intravenous fluid medium. Actual measurements of liposome dispersions in aqueous glucose solution substantiate calculations which, based on certain assumptions concerning liposome size and total liposome volume in solution, demonstrate that liposomes dispersed in a solution account for only a small fraction of the solution's osmolality. Hence, the present invention allows one to employ an encapsulated nutrient solution having a higher actual osmolality (thus increasing the caloric content per volume of the intravenous fluid) while avoiding the problems associated in the prior art with using a high osmolality alimentation solution like C-1800. In particular, it is possible, in accordance with the present invention, to overcome

the drawback of excessively high osmolality in hyperalimentation fluids by encapsulating the nutrient and, thereby, keeping the effective osmolality of the hyperalimentation fluid comparatively lower.

To appreciate another feature of the present invention, further background on the properties of liposomes is required. When injected intravenously, liposomes generally show a pronounced preference for cells comprising the reticuloendothelial system (RES), particularly in the liver and the spleen. A general discussion of the RES is given in HISTOLOGY 146-53 (L. Weiss & R. Greep eds. 1977), the contents of which are incorporated herein by reference. In the prior art, the aforementioned preference has generally been regarded as a major disadvantage, since sequestration of drug-encapsulating liposomes within the organs of the RES restricts the therapeutic availability of the encapsulated drug to target sites in other organs. Accordingly, research is continuing for ways to direct liposomes preferentially to a specific target organ, by modifying liposome size, surface charge, fluidity, etc., and by introducing molecules with a specific affinity for the target onto the liposome surface. See, e.g., Leserman et al., NATURE 288: 602-04 (1980); Gregoriadis, supra at 331-33. Also, methods have been described for "blockading" (saturating) the RES to inhibit the uptake of liposomes targeted for other tissues. See, e.g., Abra & Hunt, "Liposome Disposition In Vivo IV: The Interaction of Sequencial Doses of Liposomes Having Different Diameters," RES. COMM. CHEM. PATH. PHARM. 36: 17-31 (1982); Souhami et al., "The Effect of Reticuloendothelial Blockade on the Blood Clearance and Tissue Distribution of Liposomes," BIOCHIM. BIOPHYS. ACTA 674: 354-71 (1981).

By contrast, in accordance with another aspect of the present invention, the preferential sequestra-

tion of liposomes by the RES is actively exploited to substantial advantage. More specifically, in a preferred embodiment of the present invention, liposomes are used which are known to be taken up preferentially by RES cells and broken down intracellularly by lysosomal enzymes, thereby concentrating the encapsulated contents of the liposomes in the RES. Since RES cells are particularly capable of converting high molecular weight molecules, such as oligosaccharides, into simpler constituents which can be catabolized by other cells, the targeting of the RES in accordance with one embodiment of the present invention permits the use of larger molecules as an energy source in the encapsulated nutrient solution.

Thus, with the present invention a nutrient fraction comprising, for example, a higher saccharide like maltotetrose or maltohexose, as the high molecular weight energy-providing species can be concentrated in the RES and there broken down into glucose, which is then distributed by the RES through the bloodstream to provide needed calories to the rest of the body. By employing the RES in this fashion, both to break down and to distribute the nutrient fraction delivered via liposomes preferentially phagocytized by the RES, the present invention provides for the use of larger molecules that are less likely to leak out of the liposomes after encapsulation.

With the larger molecules it is possible to use a nutrient solution having a lower osmolality and still entrap a higher caloric value per liposome than would be possible if a solution of some simpler nutrient like glucose were used. The present invention does not require the use of larger molecules in the nutrient solution, however. A lower molecular weight nutrient, such as a monosaccharide or an amino acid, can also be utilized in accordance with the present invention,

since they are generally usable by cells in vivo without being broken down enzymatically, i.e., liposomes encapsulating a nutrient solution which contained a lower molecular weight nutrient would not have to be targeted for the RES. All that would be required would be that the liposomes be stable in the carrier medium; once in the blood, the liposomes would become unstable, by virtue of the osmolality differential, enzymatic action, and/or lipid exchange.

For example, if a liter of a 14 weight-percent (wt.%) glucose solution (about 900 mosmoles) were encapsulated by a method assuring a 50% entrapment rate, 70 grams of glucose would be contained in the liposomes. Because of its relatively high osmolality, a 14 wt.% solution is the approximate maximum glucose concentration that can be encapsulated in liposomes which are stable in liquids of like osmolality. But because there is a marked difference between the osmolality of the encapsulated solution and blood serum, these liposomes will become unstable upon introduction into the bloodstream.

On the other hand, if the 14 wt.% glucose solution were replaced with a 20 wt.% solution of maltotetrose (about 300 mosmoles), 100 gram of maltotetrose would be encapsulated at the assumed 50% entrapment rate. Accordingly, some 43% more calories would be entrapped with the maltotetrose solution than with the glucose solution, even though the former has a lower osmolality than the latter. Moreover, even higher concentrations of oligosaccharide are readily accommodated, in accordance with the present invention. As a result, liposomes encapsulating, for example, a maltotetrose solution as previously described can deliver more calories and yet remain intact (that is, will not swell under osmotic pressure and burst) when dispersed in a conventional intravenous alimentation

fluid like P-900 (approximately 900 mosmoles) prior to being introduced into the bloodstream, where the osmolality is in the range of 300 mosmoles. By using nutrient molecules of even higher moleculer weight, a nutrient solution having an osmolality substantially lower than 300 mosmoles can be prepared for encapsulation in liposomes, following the present invention. Generally, oligosaccharides having a molecular weight of less than about 5,000 may be used. An intravenous alimentation fluid of enhanced stability is thus obtained with the present invention.

Derivative compounds, for example, ionized derivatives and/or phosphotized derivatives, can also be used as nutrients.

As previously indicated, various methods are known for preparing liposomes for use in accordance with the present invention. Several suitable encapsulation techniques are described by Schneider in U.S. Patent No. 4,224,179, the contents of which are incorporated herein by reference. A preferred technique is the "reverse phase evaporation" (REV) method described by Szoka, Jr., and Papahadjopoulos, "Procedure for Preparation of Liposomes with Large Internal Aqueous Space and High Capture by Reverse-Phase Evaporation," PROC. NATL. ACAD. SCI. USA 75: 4194-98 (1978), which is also incorporated herein by reference. REV vesicles are preferentially absorbed by the RES, see Ellens et al., "Reversible Depression of the Reticuloendothelial System by Liposomes," BIOCHIM. BIOPHYS. ACTA 714: 479-85 (1982); Kao & Juliano, "Interactions of Liposomes with the Reticuloendothelial System," BIOCHIM. BIOPHYS. ACTA 677: 453-6 (1981), and are therefore especially suitable as liposome vehicles in the present invention. By the same token, it is known that the RES concentrates larger liposomes, apparently as a function of their higher total surface charge.

See, e.g., Abra & Hunt, supra. Accordingly, liposomes in the size range between about 0.2 and about 0.8 microns are generally preferred in the present invention.

It has already been noted that larger molecules can be used to advantage in the present invention as an energy source in the encapsulated nutrient solution. Suitable higher molecular weight constituents include oligosaccharides and polypeptides obtained from starch and proteinaceous material, respectively, by acidic or enzymatic hydrolysis. Typically, the starch or protein can be hydrolyzed and the resulting cleavage products then isolated according to molecular weight via column chromatography, as described by Pazur, "Oligosaccharides," in THE CARBOHYDRATES (Vol. 2-A) 61-129 (W. Pigman & O. Horton eds. 1970), and Hill, "Hydrolysis of Proteins," in ADVANCES IN PROTEIN CHEMISTRY (Vol. 20) 37 (1965), the contents of which are incorporated herein by reference. A starch-hydrolysis product which may be used in accordance with the present invention is obtainable by removing components having a molecular weight greater than about 5,000, for example, by paper filtration and Sephadex column fractionation, from a product available commercially as "dextrin, Type III" from Sigma, Inc., (St. Louis, MO). The final mixture of oligosaccharides contains compounds having a molecular weight of less than about 5,000 and less than one percent glucose. Also, the breakdown products of other polysaccharides, such as amylose, are also suitable.

In another preferred embodiment of the present invention, the caloric requirements of an intravenously-fed subject are met, either in whole or substantial part, using the liposomes themselves as nutrients. This means that a hyperalimentation fluid comprising a dispersion of liposomes which encapsulate little or no solution, i.e., which are essentially "empty" can be

used. While such "low-entrapment" liposomes contain little or no nutrient solution per se, they do comprise phospholipids that can be metabolized to provide calories when the liposomes are phagocytized by target cells in vivo.

Alimentation via intravenous delivery of a dispersion of low-entrapment liposomes, in accordance with the present invention, provides significant advantages over conventional intravenous feeding techniques as described above. For example, in the liposomes used according to the present invention, a polar lipid compound which characteristically is charged can be incorporated into the vesicular membrane. Thus, phosphotidylcholine and/or phosphotidic acid could be added, with or without cholesterol, to the liposome-forming mixture. A sufficient amount of the compound would be included such that all the liposomes in dispersion carry a surface charge, which charge tends to keep the liposomes apart in dispersion and, thereby, counteracts any tendency for liposomes to aggregate and fuse.

Thus, by adjusting the total lipid content of the dispersion, an amount of lipid comparable to that of conventional fat emulsions can be administered intravenously, in accordance with the present invention, without the above-mentioned drawbacks of aggregation and fusion of fats in the hyperalimentation fluid. It has also been discovered that the association, by ionic, lipophilic or covalent bonding, of a macromolecule with the liposome membrane counteracts the undesired aggregation phenomenon. For example, liposome aggregation in P-900 is prevented by the addition to the vesicular membranes of human serum protein, albumin or blue dextran.

Most of the lipids in conventional intravenous fat emulsions exchange with blood plasma lipoproteins in vivo. The lipid material contained in a liposomal

dispersion delivered intravenously in accordance with the present invention, however, can both be exchanged with blood plasma lipoproteins and taken up and used by the RES. The extent to which the liposomes undergo exchange with lipoproteins, rather than phagocytization by the RES, is influenced byliposome composition. For example, incorporating cholesterol into the liposomes can stabilize them against the action of blood enzymes, thereby inhibiting exchange with lipoproteins in blood plasma. Liposome size also influences exchange, since smaller vesicles are taken up more slowly by the RES and, hence, remain in the bloodstream longer. Accordingly, smaller liposomes in the size range between about 0.08 and about 0.2 microns, such as those produced by the modified REV method of Frokjaer et al, "Stability and storage of liposomes," in OPTIMIZATION OF DRUG DELIVERY (Alfred Benzon Symposium 17) 384-97 (Bundgaard et al eds. 1982), the contents of which are incorporated by reference, can be used to advantage.

Either MLV's or SUV's, or both, can be used as low-entrapment vesicles in the present invention. Since SUV's are smaller and are taken up by liver parenchymal cells as well as the RES, however, they can be used to advantage to ameliorate or eliminate RES blockade, if desired.

According to the present invention, a nutrient solution as described above is encapsulated in liposomes, the liposomes are dispersed in a sterile, physiologically compatible carrier, and the fluid is then introduced into a suitable vein via a conventional intravenous hookup. The smaller liposomes (generally, less than 1 micron in size) used in the present invention avoid the nonspecific symptoms of liposome toxicity commonly attributed to the blockage of capillaries by liposomes which exceed 1 micron in size. Although the appropriate concentration of liposomes in the

hyperalimentation fluid would be expected to vary somewhat from subject to subject, dosages of approximately 60-120 grams of liposomes per day fall within a reasonable clinical range. However, if a vesicle component associated with toxicity, such as stearylamine, is incorporated into the liposomes, a smaller dosage is indicated. Generally, saturated and unsaturated phospholipids can be used to form the liposomes, so long as the resultant vesicles display an adequate retention of any encapsulated material. Exemplary lipid materials suitable for use in the present invention include phosphotidylcholine, phosphotidic acid, cholesterol, phosphotidylethanolamine, phosphotidylserine, phosphotidylglycerol, sphingomyelin, dimyristylphosphotidylcholine, dipalmitoylphosphotidylcholine, dipalmitoylphosphotidyl glycerol, distearoylphosphotidylcholine, hydrogenated phosphotidylcholine, and phosphotidylinositol. Mixtures of phosphotidylcholine with other components, such as cholesterol or Vitamin E, are also suitable.

The composition of a hyperalimentation fluid employed in the method of the present invention would vary, depending on the amount of lipid used and the percent entrapment achieved. For example, if 25% of the final fluid volume were taken up by liposomes which contained 66 micromole of phosphotidylcholine per ml of aqueous phase and which encapsulated (at a 50% entrapment) a nutrient solution containing 25% by weight of a particular oligosaccharide, then a liter of fluid would contain approximately 62 grams of the oligosaccharide and 20 grams of lipid material. The caloric content of the liposome-based fraction of the fluid would be about 362 calories. The remaining 75% of the fluid's total volume could be made of, for example, equivolumes of a 10% glucose solution and a 9% amino acid solution. The inclusion of electrolytes

would be optional, although magnesium and calcium would not be preferred, since their presence would enhance fusion of liposomes in dispersion. With the additional caloric value of the glucose and amino acids, the total caloric content of the hyperalimentation fluid would be about 607 calories per liter.

As another example, the liposome concentration could be adjusted so that liposomes accounted for 50% of the hyperalimentation fluid's volume. If a 50% entrapment of the oligosaccharide-containing solution is assumed, then (with the same liposome preparation as in the previous example) approximately 125 grams of oligosaccharide would be encapsulated in liposomes comprising 40 grams of lipid. The caloric content of the liposome-based fraction would be from 725 calories, that of the remaining fluid about 143, and the total caloric content would be 868 calories.

WHAT IS CLAIMED IS:

1. An intravenous alimentation method for satisfying at least a substantial portion of a mammal's intravenous caloric requirements, comprising the step of introducing into the bloodstream of said mammal a hyperalimentation fluid comprising a physiologically compatible carrier having dispersed therein a nutritionally effective amount of nutrient-containing bilayer membrane vesicles.

2. An intravenous alimentation method as claimed in Claim 1, wherein said vesicles are comprised of lipid material sufficient to satisfy said substantial portion of said mammal's intravenous caloric requirements.

3. An intravenous alimentation method as claimed in Claim 2, wherein said lipid material comprises a polar lipid compound which is charged.

4. An intravenous alimentation method as claimed in Claim 2, wherein said lipid material comprises at least one substance selected from the group consisting of phosphotidylcholine, phosphotidic acid, cholesterol, phosphotidylethanolamine, dipalmitoylphosphotidylcholine, dipalmitoylphosphotidyl glycerol, distearoylphosphotidylcholine, hydrogenated phosphotidylcholine, and phosphotidylinositol.

5. An intravenous alimentation method as claimed in Claim 2, wherein said vesicles comprise multilamellar vesicles.

6. An intravenous alimentation method as claimed in Claim 2, wherein said vesicles comprise small unilamellar vesicles.

7. An intravenous alimentation method as claimed in Claim 6, wherein said vesicles range in size from about 0.02 to 0.15 microns.

8. An intravenous alimentation method as claimed in Claim 1, wherein said vesicles encapsulate a nutrient solution suitable as an intravenous caloric source for said mammal.

9. An intravenous alimentation method as claimed in Claim 8, wherein said nutrient solution comprises at least one nutrient selected from the group consisting of an amino acid, a polypeptide, an oligosaccharide, a monosaccharide, and a derivative of one of the foregoing compounds.

10. An intravenous alimentation method as claimed in Claim 9, wherein said nutrient solution comprises an oligosaccharide selected from the group consisting of maltotetrose, maltohexose, a breakdown product of starch, and a breakdown product of amylose.

11. An intravenous alimentation method as claimed in Claim 10, wherein said nutrient solution comprises maltotetrose in an amount ranging between about 20% and about 38% by weight.

12. An intravenous alimentation method as claimed in Claim 8, wherein the osmolality of said nutrient solution encapsulated in said vesicles is approximately 900 milliosmoles or less.

13. An intravenous alimentation method as claimed in Claim 8, wherein said nutrient solution comprises a breakdown product of a protein.

14. An intravenous alimentation method as claimed in Claim 13, wherein the osmolality of said

nutrient solution encapsulated in said vesicles is approximately 900 milliosmoles or less.

15. An intravenous alimentation method as claimed in Claim 8, wherein said vesicles comprise reverse phase evaporation vesicles.

16. An intravenous alimentation method as claimed in Claim 8, wherein said vesicles range in size between about 0.2 and about 0.8 microns.

17. An intravenous alimentation method as claimed in Claim 2, wherein said vesicles range in size between about 0.08 and about 0.2 microns.

18. An intravenous alimentation method as claimed in Claim 5, wherein said vesicles range in size between about 0.2 and about 2 microns.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/01621

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/50; A 61 K 31/70; A 61 K 37/02

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 9/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Chemical Abstracts, volume 99, no. 15, 10 October 1983, Columbus, Ohio (US) G. Kleinberger et al.: "General characteristics and galenic aspects of fat emulsions", see page 521, abstract 120898q, & Infusionsther.Klin.Ernaehr. Forsch.Prax. 1983, 10(3), 108-10, 112-17 (Ger.)	1-18
Y	--	1,9-11
Y	Chemical Abstracts, volume 88, no. 19, 8 May 1978, Columbus, Ohio (US) Kawaura, Yukimitsu et al.: "Parenteral hyperalimentation with saccharides during acute pancreatitis", see page 420, abstract 135221k, & Geka Shinryo 1978, 20(1), 119-22 (Japan)	1,9-11
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* Special categories of cited documents: [10]

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th December 1985	24 JAN. 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (C NTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
E	EP, A, 0162129 (THEURER) 27 November 1985, see claims; page 1, example 1	1-18

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/01621 (SA 10589)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/01/86

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0162129	27/11/85	DE-A- 3413541	17/10/85